

# Bristol-Myers Squibb Pharmaceutical Research Institute

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Laurie Smaldone, M.D.  
Senior Vice President  
Worldwide Regulatory Affairs

November 5, 1999

**Dockets Management Branch  
Food and Drug Administration, HFA-305  
5630 Fishers Lane, Room 1061  
Rockville, MD 20857**

**Re: Docket No. 97D-0433; Draft Guidance, *Average, Population, and Individual Approaches to Establishing Bioequivalence*, 64 Federal Register 48842 (September 8, 1999)**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled \$1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to issue a guidance for industry regarding average, population, and individual approaches to establishing bioequivalence. A comprehensive review of the study design and statistical analyses issues associated with each approach to demonstrating bioequivalence has been conducted by a panel of scientists from PhRMA member companies. This review has culminated in the preparation of a White Paper entitled, "PhRMA Perspective on Population and Individual Bioequivalence". Bristol-Myers Squibb is in agreement with the recommendations developed in the White Paper, and also concurs that additional discussion is warranted before implementing any changes in the current approach to evaluating bioequivalence, including the use of the standard 2 x 2 crossover trial design.

There are several aspects of the PhRMA perspective that we wish to elaborate on.

## **I. Global Harmonization**

Although the current approach for demonstrating bioequivalence is not completely harmonized

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around the world, if a study satisfies the current FDA requirements for average bioequivalence, it is usually acceptable to other health authorities. This will not be the case with individual bioequivalence, since other regulatory bodies have not expressed an interest in moving in this direction. This raises the distinct possibility that the regulatory burden will be increased, since it may become necessary to utilize one study design to satisfy the regulatory requirements in the USA and a separate study and/or analyses for other markets. Not only is this problematic from a resource perspective, but it has been shown that different conclusions may be drawn depending upon the study design and analysis plan. Therefore, the data sets used to define bioequivalence in a global setting will vary.

Recommendation: Given the pivotal role bioequivalence studies play in marketing authorization decisions, any change in design or analyses should have world-wide acceptance prior to implementation, and the process should involve the International Conference on Harmonization.

## **II. Assessment of the Subject by Formulation Interaction**

As described in the PhRMA White Paper, the clinical relevance of a subject by formulation interaction has not been shown. Although the draft guidance recommends enrollment of a heterogeneous subject population in the bioequivalence study, it is unlikely that there will be sufficient representation from a particular demographic subgroup to draw a valid conclusion regarding a subject by formulation interaction. Conversely, intrasubject variability in pharmacokinetics may be misinterpreted as a subject by formulation interaction when the number of subjects in a demographically-related group is small. Neither this draft guidance nor the draft on general considerations for bioavailability and bioequivalence studies addresses the impact of subgroup enrollment on sample size estimations or the statistical analyses of the data. This could result in the need to increase the sample size and magnify recruiting problems. We agree that in some cases it may be advantageous to study bioequivalence in the population of patients who will be treated with the drug; however, even in these situations the inclusion/exclusion criteria will need to be defined to ensure a certain consistency in baseline characteristics. It is further noted that the current EMEA guidance on the investigation of bioavailability and bioequivalence recommends selection of a subject population that minimizes variability, generally consisting of healthy volunteers of either gender between 18 – 55 years of age.

Recommendation: In order to make section VB of the draft guidance as clear as possible, the use of the phrase “a reasonable balance” should be removed and replaced by the following sentence: Sponsors are encouraged to enroll as heterogeneous a study population as possible, consistent with the primary objectives of the study.

## **III. Resource and Ethical Considerations**

Replicate designs increase subject risk by doubling the number of exposures to a drug, as well as the number of blood samples drawn from each volunteer. The costs associated with running a bioequivalence study using a replicate design are also likely to increase, both from a dollar (more safety assessments per subject, longer stays in the clinical facility, more subjects enrolled to safeguard against dropouts) as well as from a time (more sessions per subject increase study duration) perspective. The tables in Appendix C (Sample Size Determination) of the draft guidance suggest that drugs with low to moderate within- and between-subject variabilities require a greater number of subject dosing sessions to demonstrate bioequivalence using the individual, compared to

the average, approach. Additionally, in a study analyzed using individual bioequivalence, the number of dosing sessions is generally increased, even though the number of subjects may be less. Therefore, using a replicate study design for the evaluation of either average or individual bioequivalence will be associated with these resource and ethical considerations.

#### **IV. Data Collection Period**

There are many unanswered questions with respect to the management of the 2-year interval over which the Agency wants sponsors to gather data using replicate designs, even if this is restricted to modified release products. For example, what will the impact be on compounds already in development and scheduled to be filed during the 2-year interval (both NDA and SNDA)? Also, will the FDA require an agreement on the design elements prior to study initiation, which could adversely effect development timelines? Without a clear definition of expectations, time will be needlessly wasted on study by study negotiations.

Recommendation: As suggested by PhRMA, the details of the 'further study period' should be developed in a workshop setting that enables participation from pharmaceutical scientists representing the global industrial, academic, and regulatory communities.

Bristol-Myers Squibb appreciates the opportunity to provide comment and respectfully requests that FDA gives consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

A handwritten signature in cursive script, appearing to read "Laurie Smaldone", followed by a horizontal line.

Laurie Smaldone, M.D.  
Senior Vice President  
Regulatory Science & Outcomes Research



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